REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 48-50, 55, 62-64 and 68 are in the case.

I. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 48-50, 55, 62-64 and 68 stand rejected under 35 U.S.C. §112, first paragraph, on the ground that the specification, at the time the application was filed, is allegedly not enabling in that it would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without the exercise of undue experimentation. The rejection is respectfully traversed.

At the outset, the position taken in the present Action is inconsistent with that previously taken by the Office during prosecution of this case. Thus, in the Action mailed on October 22, 2003, the Office rejected claims 48-59 and 62-68 on lack of enablement grounds, asserting that the specification, "while **enabling**" (emphasis added) for the treatment of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction, allegedly did not reasonably provide enablement for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction. (Official Action, mailed 10/22/03, page 4).

In response to that 2003 rejection, applicants amended their claims to remove the references to "prevention" of the recited condition. Based on that amendment, the

lack of enablement rejection was withdrawn in the immediately following Action mailed September 9, 2004.

The position now taken by the Office is contrary to the position taken in October, 2003. In October, 2003, the Office admitted that claims to the "treatment" of the recited conditions were enabled and, in reliance, Applicants amended their claims by deletion, without prejudice, of the prevention aspect of their invention. To now assert lack of enablement of the claims directed to the treatment of the recited conditions is not justified by any new reasoning or evidence reflected in the prosecution history of this case. Withdrawal of the lack of enablement rejection on this ground is respectfully requested.

The outstanding Action asserts that:

> "At the time of the invention, the treatment of mitochondrial disorders was ineffective. There were no correlations between treatment regimens and therapeutic responses to disorders. Treatment was unpredictable and heterogenous. The examiner directs applicant to PRZYREMBEL *J. Inher. Metab. Dis.* (1987), Vol. 10, pages 129-146 (PRZYREMBEL). PRZYREMBEL teaches, 'Mitochondrial disorders, namely defects of fatty acid oxidation, defects of pyruvate metabolism and defects of the respiratory chain are heterogenous in clinical picture and in response to therapeutic attempts. Defects of fatty acid metabolism are amenable to therapy by dietary means, carnitine substitution and in some cases with vitamins. Defects in pyruvate metabolism do not respond to therapy except in some special cases. Therapeutic attempts include dietary measures, vitamins as coenzyme precursors. Defects in the respiratory chain appear to respond to treatment only in exceptional cases. Evaluation of treatment effects appears to be singularly difficult.' See Abstract." (Official Action, page 5, first complete paragraph)

The reliance on Przyrembel *J. Inher. Metab. Dis.* (1987), Vol. 10, pages 129-146 (Przyrembel) in support of a lack of enablement rejection is misplaced. At the outset, it is noted that Przyrembel was published in 1987, approximately eight years before the

priority date of the present application and at a very early stage in the understanding of mitochondrial diseases and their treatment. Significant progress has been made since 1987 in the understanding of mitochondrial disease and its treatment. In this regard, attention is directed to the Amendment dated October 7, 2005 and the accompanying IDS, which listed (and was accompanied by a copy of), *inter alia*, a reference to DiMauro *et al.*, "Mitochondrial Encephalomyopathies: Where Next?" (1999) *Revista De Neurologia*, 28(2):164-168. In that reference, it is stated at page 2:

> "Although mtDNA was discovered 36 years ago (Nass and Nass 1963) and human mtDNA had been fully sequenced by 1981 (Anderson, et al. 1981), clinicians paid no attention to this genetic relic until **1988**, when mutations in mtDNA were first associated with human disease; (Holt, et al. 1988, Wallace, et al, 1988). In the intervening years, however, a cadre of scientists had worked hard at clarifying the organization of the mitochondrial genome and the peculiar rules governing its replication, transcription, and translation (Schon 1997).....As the title of this chapter implies, we will not even attempt to review the **enormous progress achieved** in the 38 years since Luft and coworkers introduced the concept of mitochondrial disease, nor even **in the 12 years since the description of pathogenic mtDNA mutations**." (Emphasis added)

In light of the above, it is clear that one of ordinary skill would not have viewed Przyrembel (1987) as indicative of the state of the art against which the presently claimed invention should be gauged. DiMauro (1999) notes the "enormous progress" made since Luft's initial work and one of ordinary would have been aware of this as of the filing of the present application. Although DiMauro was published about one year after the priority date of the subject application, DiMauro is evidence of developments in the art during the period between publication of Przyrembel (1987) and the priority date of the subject application. Moreover, Examples 1, 3, 7, 8 and 9 of the present application all deal with respiratory chain defects and further support enablement of the

invention as claimed. Thus, any assertion that it is "only in exceptional cases" (Official Action, page 5, first complete paragraph) that defects in the respiratory chain appear to respond to treatment is no longer true in light of the instant invention. The person of ordinary skill in the art, upon reading the specification of the subject application, would consider any such statement in Przyrembel to have been superseded. For these further reasons, it is believed that the lack of enablement rejection should be withdrawn.

Finally, in an effort to progress prosecution, the claims have been amended without prejudice to specify that the pyrimidine nucleotide precursor is selected from uridine, an acyl derivative of uridine, cytidine and an acyl derivative of cytidine. Basis appears in the originally filed application at pages 7 and 8. No new matter is entered. Withdrawal of the lack of enablement rejection is now in order, and is requested.

II. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claim 55 stands provisionally rejected on obviousness-type double patenting grounds as allegedly unpatentable over claims 31, 32 and 38-41 of copending Application Serial No. 09/930,494. Applicants will consider filing a Terminal Disclaimer when otherwise allowable subject matter is indicated.

Favorable action is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100